REMARKS

Claims 1-48 are pending and are the subject of the present Office Action. In the Office Action mailed September 28, 2001, the Examiner issued a Restriction Requirement under 35 USC 121, requiring restriction to one of Groups I-VII. Applicants hereby elect to prosecute in the present application the inventions embodied by the claims of Group I identified by the Examiner. The species relating to zinc are hereby elected. Claims 1-12 and 49-60 are believed to read on the elected species. Claims 13-48 have been canceled without prejudice in the above amendment as being drawn to the non-elected inventions. Applicants do preserve the right to pursue claims directed to the non-elected inventions in further continuing applications.

Claims 49-60 have been added. Support for the added claims can be found on at least pages 12-17 and 37 of the specification.

The specification has also been amended to correct certain inadvertent typographical errors in various reference citations. It is submitted that no new matter has been introduced by these amendments.

The amendments to the specification and claims are illustrated on the attached pages entitled "Marked Up Version to Show Changes Made". For the Examiner's convenience, a clean copy of all the now pending claims 1-12 and 49-60 is provided above.

Respectfully submitted,

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By: Diane L. Marschang
Diane L. Marschang
Reg. No. 35,600

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-5416
Fax: (650) 952-9881

Marked Up Version to Show Changes Made

In the specification:

On page 7, in the paragraph on lines 7-22, the text has been amended as follows:

---While zinc binding sites have been shown to play structural roles in protein-protein interactions in certain proteins involving diverse interfaces [Feese et al., Proc. Natl. Acad. Sci., 91:3544-3548 (1994); Somers et al., Nature, 372:478-481 (1994); Raman et al., Cell, 95:939-950 (1998)], none of the previously structurally-characterized members of the TNF family (CD40 ligand, TNF-alpha, or TNF-beta) bind metals. The use of metal ions, such as zinc, in formulations of various hormones, such as human growth hormone (hGH), has been described in the literature. [See, e.g., WO 92/17200 published October 15, 1992). Zinc involvement in hGH binding to receptors was likewise described in WO 92/03478 published March 5, 1992. The roles of zinc binding in interferon-alpha dimers and interferon-beta dimers were reported in [Walter] Radhakrishnan et al., Structure, 4:1453-1463 (1996) and Karpusas et al., Proc. Natl. Acad. Sci., 94:11813-11818 (1997), respectively. ---

On page 51, in the paragraph on lines 6-29, the text has been amended as follows:

---pAPApo2-P2RU (see Figure 12) encodes for the co-expression of Apo-2L (amino acid residues 114-281) and the tRNA's encoded by *pro2* and *argU*. The pBR322-based plasmid [Sutcliffe, Cold Spring Harbor Symp. Quant. Biol., 43:77-90 [(1978)] (1979)] pAPApo2-P2RU was used to produce the Apo-2L in *E. coli*. The transcriptional and translational sequences required for the expression of Apo-2L are provided by the alkaline phosphatase promoter and the *trp* Shine-Dalgarno, as described for the plasmid phGH1 [Chang et al., Gene, 55:189-196 (1987)]. The coding sequence for Apo-2L (form 114-281) is located downstream of the promoter and Shine-Dalgarno sequences and is preceded by an initiation

methionine. The coding sequence includes nucleotides (shown in Figure 1) encoding residues 114-281 of Apo-2L (Figure 1) except that the codon encoding residue Pro119 is changed to "CCG" instead of "CCT" in order to eliminate potential secondary structure. The sequence encoding the lambda to transcriptional terminator [Scholtissek et al., Nucleic Acids Res., 15:3185 (1987)] follows the Apo-2L coding sequence. Additionally, this plasmid also includes sequences for the expression of the tRNA's *pro*2 [Komine et al., J. Mol. Biol., 212:579-598 (1990)] and *argU/dnaY* [Garcia et al., Cell, 45:453-459 (1986)]. These genes were cloned by PCR from *E. coli* w3110 and placed downstream of the lambda to transcriptional terminator sequence. This plasmid confers both tetracycline and ampicillin resistance upon the production host. ---

In the claims:

Please cancel claims 13-48 without prejudice.

Please add the following claims:

---49. A formulation comprising Apo-2 ligand and one or more divalent metal ions, wherein the concentration of said one or more divalent metal ions present in the formulation is at a <2X molar ratio to said Apo-2 ligand and the Apo-2 ligand comprises a polypeptide selected from the group consisting of:

(a) a polypeptide having amino acid residues 1 to 281 of Figure 1 (SEQ ID NO:1);

(b) a polypeptide having amino acid residues 114 to 281 of Figure 1 (SEQ ID NO:1);

(c) a fragment of the polypeptide of (a) or (b) which induces apoptosis in at least one type of mammalian cell or binds an Apo-2 ligand receptor; and

(d) a polypeptide having at least 80% identity to the polypeptide of (a) or (b), and induces apoptosis in at least one type of mammalian cell or binds an Apo-2 ligand receptor.

50. The formulation of claim 49 wherein said one or more divalent

metal ions comprises zinc.

51. The formulation of claim 50 wherein said zinc is selected from the group consisting of zinc chloride, zinc acetate, zinc sulfate, zinc carbonate, and zinc citrate.

52. The formulation of claim 49 wherein said formulation has a pH of about 6 to about 9.

53. The formulation of claim 49 wherein said formulation has a pH of about 7 to about 7.5.

54. The formulation of claim 49 wherein said formulation is a lyophilized formulation.

55. A formulation comprising Apo-2 ligand and one or more divalent metal ions, wherein the concentration of said one or more divalent metal ions present in the formulation is at a $\geq$2X molar ratio to said Apo-2 ligand and the Apo-2 ligand comprises a polypeptide selected from the group consisting of:
(a) a polypeptide having amino acid residues 1 to 281 of Figure 1 (SEQ ID NO:1);
(b) a polypeptide having amino acid residues 114 to 281 of Figure 1 (SEQ ID NO:1);
(c) a fragment of the polypeptide of (a) or (b) which induces apoptosis in at least one type of mammalian cell or binds an Apo-2 ligand receptor; and
(d) a polypeptide having at least 80% identity to the polypeptide of (a) or (b), and induces apoptosis in at least one type of mammalian cell or binds an Apo-2 ligand receptor.

56. The formulation of claim 55 wherein said one or more divalent metal ions comprises zinc.

57. The formulation of claim 56 wherein said zinc is selected from

the group consisting of zinc chloride, zinc acetate, zinc sulfate, zinc carbonate, and zinc citrate.

58. The formulation of claim 55 wherein said formulation has a pH of about 6 to about 9.

59. The formulation of claim 55 wherein said formulation has a pH of about 7 to about 7.5.

60. The formulation of claim 55 wherein said formulation is a suspension formulation. ---